Tetrahedron Letters 57 (2016) 4395–4397

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Convenient modular construction of medicinally important 5-acylamino-4,5-dihydroisoxazoles featuring four elements of diversity

Alexandra Kulyashova, Mikhail Krasavin *

Saint Petersburg State University, 7/9 Universitetskaya nab., St. Petersburg 199034, Russia

ARTICLE INFO

Article history:
Received 18 July 2016
Revised 14 August 2016
Accepted 18 August 2016
Available online 20 August 2016

Keywords:
Enamide
Nitrile oxide
1,3-Dipolar cycloaddition
Modular synthesis
Multicomponent reactions
Isoxazolines
Privileged structures

ABSTRACT

An efficient modular approach toward medicinally important 5-acylamino-4,5-isoxazolines via the 1,3-dipolar cycloaddition reaction of nitrile oxides and MCR-derived enamide building blocks is described. This approach results in isoxazolines containing four elements of diversity utilizing two practically simple synthetic operations.

Synthetic methods that deliver, within a number of convergent steps, medicinally important scaffolds while allowing for full and independent control over the peripheral moieties, are of particular importance to medicinal chemistry research.[1] Such methods enable the time- and cost-efficient synthesis of lead compound analogs which is a pre-requisite to understanding structure–activity relationships[2] as well as offering a clear advantage over traditional linear sequences which typically involve scaffold decoration with appendages in the last step.

Multicomponent chemistry provides a uniquely suitable toolbox for the development of such methods. Indeed, the nature of the molecular scaffold is determined by the specific multicomponent reaction (MCR) as well as various skeleton-defining post-MCR modifications, while the periphery—by a specific selection of reagents for the synthetic array. Prominent MCRs such as the Ugi[3] or Castagnoli-Cushman[4] reactions have a large enough scope to permit a wide range of side-chain variations. Strategies based on sequential MCRs introduce even more diversity elements which can be altered to fine-tune the compounds' desired biological activity and suppress side-effects.[5]

Isoxazolines certainly deserve to be considered as privileged cores[6] for drug design, taking into account the multitude of biological targets, including tyrosine phosphatase 1B,[7] macrophage migration inhibitory factor (MIF),[8] fatty acid amide hydrolase (FAAH),[9] and M_1 muscarinic acetylcholine receptors,[10] which are perturbed by isoxazoline-based compounds. Replacement of the carbohydrate portion of nucleosides with an isoxazoline core delivered nucleoside analogs that inhibited viral reverse trascriptase.[11,12] Furthermore, isoxazolines[13,14] are amide bond bioisosteres and, therefore, are useful in peptidomimetic design.[15]

One of the most popular ways to construct the isoxazoline core is the 1,3-dipolar cycloaddition of nitrile oxides with a carbon–carbon double bond.[16] The cycloaddition is particularly facile for electron-rich olefins such as enamides, which can be prepared by a range of methods.[17] Notably, enamides **1** were discovered to be principal by-products in β-lactam syntheses via ketene-imine [2+2]-cycloaddition reactions involving α-C–H imines. Presumably, this process occurred via the reaction of imines with an acyl chloride from which a ketene is generated (Scheme 1A).[18–21] Recently, we observed a similar formation of enamides **2** when attempting a Castagnoli-Cushman reaction of α-C–H imines with dicarboxylic acid anhydrides[22] which are also strong acylating agents (Scheme 1B). Upon reviewing the literature, it became apparent that the reaction of acyl chlorides with α-C–H imines in the presence of a tertiary amine HCl scavenger has gained prominence as a three-component synthesis of enamides from aldehyde precursors, with the interim formation of the respective imine intermediates.[23–27]

* Corresponding author. Tel.: +7 931 3617872; fax: +7 812 428 6939.
E-mail address: m.krasavin@spbu.ru (M. Krasavin).

http://dx.doi.org/10.1016/j.tetlet.2016.08.059
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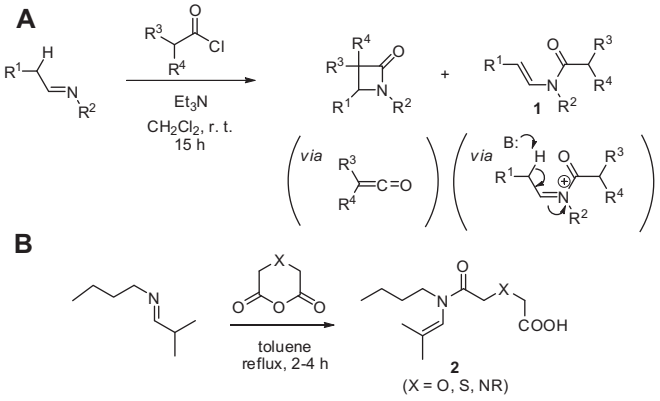


Scheme 1. Formation of enamides **1** and **2** in reactions involving α-C–H imines and the use of acylating agents.

To our surprise, however, literature regarding the construction of isoxazoles via 1,3-dipolar cycloaddition mostly described the use of readily available *N*-vinylpyrrolidone[8,10,28] or *N*-vinylphthalimide,[8] except for an isolated report describing the use of a cyclic enamide synthon[29] and a recent example involving enamides akin to **1**, generated via a base-promoted isomerization of *N*-allylamides.[30] Thus, it appeared that a modular approach (Fig. 1) to constructing isoxazolines from enamide building blocks with three independently variable elements of diversity has not been investigated in connection with said three-component approach. Herein, we report recent results from our laboratories that fill this void.

Five exemplary enamides **3a–e** were prepared[31] from their respective aldehydes and primary amines via the intermediate formation of an imine intermediate using $MgSO_4$ as a dehydrating agent. The crude imine was treated with acyl chlorides in the presence of triethylamine ($MgSO_4$ was added to suppress possible enamide hydrolysis by adventitious water). Formation of **3a–e** was complete within 2–18 h according to the ^{1}H NMR spectroscopic analysis of reaction mixture aliquots (Scheme 2).

While the crude enamides were at least 85% pure by ^{1}H NMR spectroscopy, attempted use of this material in subsequent cycloaddition reactions unexpectedly delivered a complex mixture of products. Therefore, enamides **3a–e** were purified by chromatography using eluents containing triethylamine to neutralize the slightly acidic silica gel (ESI). Despite this precaution, the isolated yields of **3a–e** were somewhat modest (Table 1).

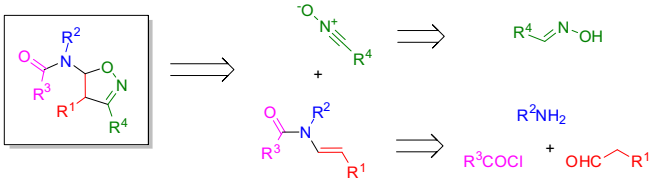
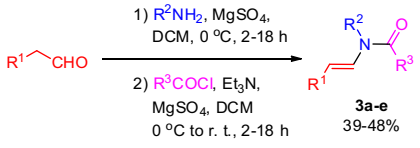


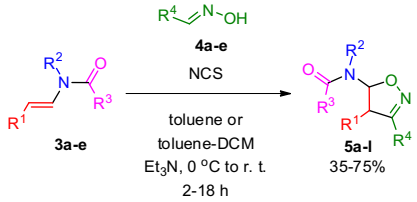
Figure 1. Modular approach to constructing 5-acylaminoisoxazolines from MCR-derived enamides envisioned and realized in present study.



Scheme 2. Three-component synthesis of enamides **3a–e**.

Table 1
Enamides **3a–e** prepared via a three-component approach

Compound	R^1	R^2	R^3	Isolated yield **3** (%)
3a	H	Bn	Ph	42
3b	Me	Bn	Ph	39
3c	H	4-$MeC_6H_4CH_2$	4-$O_2NC_6H_4$	48
3d	H	$MeO(CH_2)_3$	4-MeC_6H_4	46
3e	H	3-$PyCH_2$	Ph	41



Scheme 3. Preparation of 5-acylamino-4,5-isoxazoles **5a–l** via 1,3-dipolar cycloaddition of nitrile oxides (generated in situ from oximes **4a–e**) and enamides **3a–e**.

Nitrile oxides were generated in situ, from a set of known aldoximes **4** upon treatment with *N*-chlorosuccinimide and subsequent Et_3N-promoted elimination of HCl, in the presence of enamides **3** (Scheme 3).[32]

Continuing the reaction for 2–18 h (depending on the substitution pattern in **3** and **4**, ESI) led to the formation of a single major product and a number of minor by-products. Chromatographic isolation of the major product provided the desired isoxazolines **5a–l** in modest to good yields (Table 2). The identity of these compounds was established by ^{1}H and ^{13}C NMR spectroscopy as well as high-resolution mass-spectrometry data (ESI). It should be noted that, owing to the concerted nature of the 1,3-dipolar cycloaddition process, compound **5e** was obtained as a single *cis*-isomer.

In summary, we have described an efficient modular approach toward medicinally important 5-acylamino-4,5-isoxazolines employing the 1,3-dipolar cycloaddition reaction of nitrile oxides with MCR-derived enamide building blocks, resulting in the target compounds containing four elements of diversity, utilizing two practically simple synthetic operations. This finding will facilitate the medicinal chemistry optimization of bioactive chemical series based on the 5-acylamino-4,5-isoxazoline scaffolds as it permits the independent variation of each peripheral group to explore structure–activity relationships.

Table 2
5-Acylamino-4,5-isoxazolines **5a–l**

Compound	R^1	R^2	R^3	R^4	Isolated yield **5** (%)
5a	H	Bn	Ph	Et	44
5b	H	Bn	Ph	4-MeC_6H_4	65
5c	H	Bn	Ph	4-$MeOC_6H_4$	74
5d	H	Bn	Ph	2-thienyl	44
5e	Me	Bn	Ph	4-MeC_6H_4	23
5f	H	4-$MeC_6H_4CH_2$	4-$O_2NC_6H_4$	Et	69
5g	H	4-$MeC_6H_4CH_2$	4-$O_2NC_6H_4$	4-$MeOC_6H_4$	75
5h	H	$MeO(CH_2)_3$	4-MeC_6H_4	Et	40
5i	H	3-$PyCH_2$	Ph	4-MeC_6H_4	49
5j	H	3-$PyCH_2$	Ph	4-$MeOC_6H_4$	70
5k	H	3-$PyCH_2$	Ph	3-(PhO)C_6H_4	52
5l	H	3-$PyCH_2$	Ph	2-thienyl	35

Acknowledgements

We gratefully acknowledge support from the Russian Scientific Fund (Project Grant 14-50-00069). NMR and mass spectrometry studies were performed at the Research Centre for Magnetic Resonance, the Centre for Chemical Analysis and Materials Research of Research park of Saint Petersburg State University.

Supplementary data

Supplementary data (NMR spectra of the reaction products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.059.

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31. *General procedure for the preparation of compounds* ***3a–e:*** A mixture of amine (10.0 mmol) and $MgSO_4$ (1.0 g) in CH_2Cl_2 (100 mL) was stirred at 0 °C for 5 min. Aldehyde (20.0 mmol) was added and stirring continued for 2–18 h with occasional monitoring of the reaction progress by ^1H NMR. Upon reaction completion, $MgSO_4$ was filtered off and the filtrate concentrated under reduced pressure to afford the crude imine. This was dissolved in CH_2Cl_2 (100 mL) or toluene (100 mL), then Et_3N (10.0 mmol) and $MgSO_4$ (1.0 g) were added and the mixture cooled to 0 °C. After stirring briefly (5 min), the acyl chloride (5.00–20.0 mmol, ESI) was added, the reaction allowed to reach ambient temperature and stirring continued for 2 h. The resulting precipitate was filtered off and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica using an appropriate mixture of petroleum ether/ethyl acetate/TEA (ESI) as eluent to afford the desired enamides **3a–e**.
32. *General procedure for the preparation of compounds* ***5a–l:*** NCS (220 mg, 1.65 mmol or 300 mg, 2.25 mmol, ESI) was added in one portion to a solution of the aldoxime (1.10 mmol or 1.50 mmol, ESI) in toluene or DCM (15 mL) at rt and the reaction mixture stirred for 2–18 h with occasional monitoring of the reaction progress by TLC. The succinimide precipitate was filtered off and a solution of enamide (1 mmol) in toluene or DCM (15 mL) was added over 5 min at 0 °C. A solution of Et_3N (1.50 mmol) in toluene (0.8 mL) was then added dropwise and the mixture stirred at rtfor 2–18 h. The resulting precipitate was filtered off and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica using an appropriate mixture of petroleum ether/ethyl acetate as eluent to afford isoxazolines **5a–l**.